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Successful Treatment of Cryptococcal Meningitis with Voriconazole in a Kidney Transplant Recipient

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Background: Current treatment for *cryptococcal* (C) meningitis consists in an initial course of amphotericin B (AMPHO B) combined with Flucytosine (5-FC) for two weeks, followed by an oral suppressive therapy with Fluconazole (FLU).
Objectives: We report the case of a kidney-transplant recipient successfully treated with Voriconazole (VOR) for C meningitis.
Case: Four years after kidney transplantation a 42-y-old woman was admitted with a 3 month history of headache, and a 3 week history of nuchal rigidity, double vision, memory loss and fever. Immunosuppression consisted of sirolimus/azathioprine, changed to sirolimus/prednisone when C meningitis was diagnosed. Additionally, recurrent episodes of hemolytic uremic syndrome were treated by plasmapheresis. White blood-cell count and CRP were normal, however CD4 cells were reduced (196 cells/uL). Cerebrospinal Fluid (CSF) analysis showed an elevated intracranial pressure, elevated leukocytes (8/ul), protein (1419 mg/l) and lactate (5.2 mmol/l) and a low glucose (<0.5 mmol/l). India ink preparation and CSF culture were positive for *C. neoformans*. C antigen was 1:128 in serum and 1:512 in CSF. MICs for AMPHO B were 0.5 mg/l, for FLU 8 mg/l and for VOR 0.064 mg/l. Blood cultures remained negative. Antifungal therapy with AMPHO B and 5-FC was initiated. Due to a rash, 5-FC was stopped after 2 days. 10 days later, CSF cultures remained positive but clinical symptoms had resolved. AMPHO B was replaced by oral VOR because of the good penetration into CSF and the relative high MIC of FLU. CSF concentrations of VOR were between 0.75 and 1.47 mg/l. As cultures still were positive after 5 weeks of therapy, VOR was replaced by liposomale AMPHO B for another two weeks. Under this regimen CSF cultures still remained positive and serum C antigen rose from 1:128 to 1:1024. Therefore, therapy was changed back to VOR. Finally, ten weeks after antifungal therapy was started, cultures became negative and CSF antigen (1:64) as well as serum antigen (1:128) decreased. After 18 months of treatment with VOR CSF and serum C antigen became undetectable.
Conclusions: We demonstrate successful treatment of C meningitis with oral VOR in an immunocompromised patient. Of interest, an increase of C antigen was noted under monotherapy with liposomale AMPHO B. Our patient showed a rapid clinical response to the antifungal treatment, while lacking in microbiological response as CSF cultures remained positive for ten weeks.

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Cytomegalovirus (CMV) Specific T Cells in a Liver Transplant Recipient with Severe CMV Retinitis and Immune Reconstitution Syndrome

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Background: Since CMV seronegative recipients of seropositive organ transplants are at high risk for CMV infection and disease they qualify for prophylaxis using oral ganciclovir (GCV) or valGCV. Albeit rare, the occurrence of GCV-resistant CMV strains under treatment warrants the intravenous application of foscarnet as well as dose reductions of the immunosuppressive drugs use to prevent graft rejection. Paradoxically, the recovery of immune functions may result in a worsening of the clinical symptoms referred to as immune reconstitution syndrome (IRS). IRS is a well-known phenomenon in HIV infected patients initiating HAART, but has only rarely been described in patients following solid organ transplantation.
Objectives: We report a case of GCV-resistant primary CMV infection early after liver transplantation with severe bilateral CMV retinitis.
Methods: CMV-antigenemia, CMV IgG/IgM titers and quantitative CMV PCR measurements were carried out following standard procedures. Peripheral blood mononuclear cells (PBMC) were stimulated with viral protein (CMV lysat, pp72, pp65), and SEB as a positive control. CMV specific interferon gamma (IFNγ) production of CD4+ and CD8+ T cells was measured by intracellular staining and flow cytometry analysis. Localization of the GCV-induced viral phosphotransferase (UL97) mutation was determined by real-time PCR.
Results: A CMV seronegative recipient of a CMV seropositive liver transplant was treated with oral valGCV for the first three months posttransplant.

One week after withdrawal of valGCV, she developed primary CMV infection with pp65 antigenemia (1200/250,000 leukocytes). Response to intravenous treatment with GCV was slow with persisting viral replication. A mutation of the viral phosphotransferase (UL97) was detected. CMV replication and viremia became undetectable after reduction of immunosuppression in combination with continuing valGCV treatment. The peripheral lymphocyte counts increased, but the patient developed visual disturbances. A diagnosis of severe bilateral CMV retinitis was made and a therapy with foscarnet and eventually cidofovir was initiated. Although CMV retinitis was controlled, 4 month later vitrectomy became necessary due to retinal detachment. CMV replication recurred to low but detectable (5629 c/ml). The frequency of IFNγ-producing CMV specific CD4+ and CD8+ T cells after stimulation in vitro with CMV lysate was 0.365% and 0.245%, with CMV pp65 peptide pools 0.19% and 0.085%, respectively. Remarkably, the IFNγ-response to CMV pp72 (IE1) was 0.235% in CD4+, but 4.675% in CD8+ T cells (Figure 1).

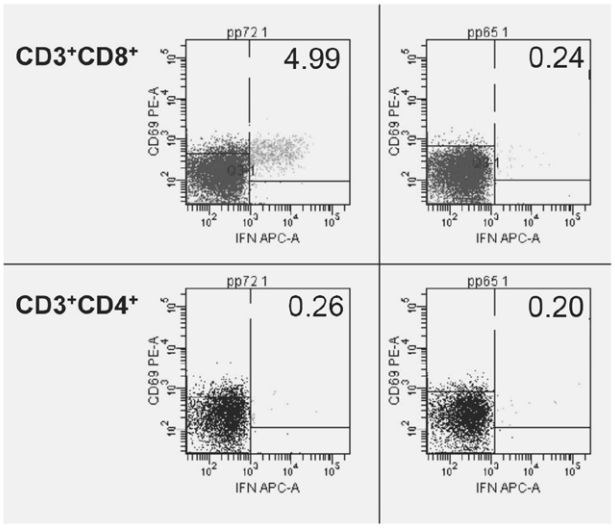

Fig. 1.

Conclusion: In this patient, the clinical signs of retinitis followed reduced immunosuppression, recovery of lymphocyte counts and the mounting of a highly selective pp72 CD8+ T cell response that was unmatched by a corresponding CD4+T-cell response. A prominent pp72 specific CD8+ T cell response without balancing CD4+ T-cells might provide an immunological correlate CMV-specific IRS. In such a situation, the use of steroids needs to be evaluated.

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Oral *Candida* Colonization in Solid Organ Transplant Recipients

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Background: Oral *Candida* colonization has been reported to be associated with a greater risk for esophagitis and pneumonitis in solid organ transplant recipients; however a systematic analysis of the oral *Candida* titers and species has not been previously conducted in this population. The objectives of this study were to determine the prevalence of oropharyngeal candidiasis and to define the oral carrier status, *Candida* titers and species in this population.
Methods: 63 kidney and heart transplant subjects were recruited from Hartford Hospital using the following criteria: 1. clinically stable; 2. at least one year post transplant; 3. no history of antifungal or antibiotic use within the last 4 months. Control subjects (n = 30) were age- and sex-matched, systemically healthy individuals. Subjects received an oral clinical examination. Swabs from the oral mucosa and a standardized amount of unstimulated saliva were plated on Chromagar® plates, and CFU/ml were calculated. Initial speciation was based on colony color and was confirmed by standard germination and biotyping (carbohydrate assimilation) assays.
Results: 1 of 63 transplant and 0 of 30 control subjects had oral infection with *C. albicans*. A significantly higher frequency of asymptomatic colonization was noted in transplant recipients (57.1%) compared to healthy controls (36.6%). In addition, the transplant group had significantly higher *Candida* titers than the control group. 83.3% of the transplant carriers were colonized by *C. albicans*, 16.6% by *C. glabrata* and 1% by *C. lusitaniae*. 22.2% of transplant carriers were colonized by more than one species, with the most frequent combination being *C. albicans* and *C. glabrata*. 81% of the control carriers were colonized by *C. albicans*, 0% by *C. glabrata* and 18% by *C. lusitaniae*. None of the control subjects were colonized by more than one species. The prevalence of xerostomia did not differ between test and control groups but the prevalence of diabetes was significantly higher in the transplant group.
Conclusions: Increased oral *Candida* carriage rate and titers were found in solid organ transplant subjects who are at least one year post-transplant. Although the majority of these subjects are colo-